REMARKS

The Office Action mailed May 29, 2002 has been received and reviewed. Claims 1-11, 14-19 and 21-23 are currently pending in the application. All claims stand rejected. Applicants have amended claims 8, 11 and 15 as set forth herein. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Applicants have also amended Figures 4-6 in accordance with the Examiner's suggestions. Submitted herewith is a letter to the Chief Draftsman directing entry of the amended figures.

Priority Document

Applicants' representatives have requested the priority document and will forward the priority document to the Examiner as soon as it received.

Objections to Drawings

The drawings, Figures 4-6, were objected to because the label "0" for the right column in each figure was thought to be confusing. The data expressed in the column was thought to be a negative control and should be labeled as such. Additionally, Figure 4 contained a number "5" below Figure 4 which was thought to be misplaced. Enclosed herewith are amended drawings, wherein the "0" is deleted from FIG. 4 and the negative control columns of Figures 4-6 are labeled as such. Reconsideration and withdrawal of the objections is thus requested.

Objections to Claims

Claim 8 was objected to because the text of claim 8 appeared to depend from claim 7 instead of claim 6. Claim 8 has been amended to depend from claim 7. Reconsideration and withdrawal of the objection are requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11 and 15-19 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicants regard as their invention. Applicants have amended claims 11 and 15, and in view of the amendments respectfully traverse the rejections.

Specifically, it was thought that claims 11 and 15-19 were indefinite because the steps recited by the methods did not achieve the goal set forth in the claim preamble. Claims 11 and 15-19 were also rejected because it was thought to be unclear what "a series of compounds" or "each element of said series of compounds" meant. Although applicants do not agree with the Examiner that the claims are indefinite as written, claims 11 and 15 have been amended to expedite prosecution of the application. Reconsideration and withdrawal of the rejections are thus requested.

Rejections under 35 U.S.C. § 103

Claims 1-6, 14 and 21-23

Claims 1-6, 14 and 21-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Muthukumaran et al. (*IDS, J. Biol. Chem.* 272: 4993-4999, 1997) in view of Trueheart et al. (*IDS*, WO 98/13513, April 2, 1998). Applicants respectfully traverse the rejections as hereinafter set forth.

The combination of Muthukumaran et al. with Trueheart et al. would appear to be improper because no suggestion or motivation exists in the cited references to combine them as suggested in the Office Action. The Office Action indicates that the motivation for the combination is "because endogenous expression of polypeptides in a cDNA library allows rapid screening of large numbers of polypeptides as taught by Trueheart et al." (Office Action, page 5). However, the statement in the Office Action does not provide a motivation to combine Trueheart et al. with Muthukumaran et al., but is merely a benefit stated in Trueheart et al. (*See*, Trueheart et al., page 3).

The combination of the cited references also appears to be based on improper hindsight reasoning using the applicants' disclosure. Since functional chimeric receptors have been known in the art before the publication date of Muthukumaran et al. (*See, e.g.*, EP 0244221, 1987) and were familiar to those skilled in the art as of the publication date of Trueheart et al., it would not have been obvious to combine chimeric receptors with the screening method of Trueheart et al.

If the idea of combining chimeric receptors with autocrinic loops were obvious, Trueheart et al. would have cited the use of chimeric receptors in the extensive disclosure.

Trueheart et al. discloses the expression of polypeptides from a library in a cell to identify polypeptides that agonize or antagonize receptor bioactivity, thus creating an autocrine system. However, no suggestion or motivation exists in Trueheart et al. to use a chimeric receptor.

With respect to Muthukumaran et al., no suggestion or motivation exists to combine a eukaryotic cell comprising the chimeric receptor with a library of polypeptides and a reporter system Trueheart et al. Rather, Muthukumaran et al. is limited to the study of the structure of chimeric receptor complexes, and does not disclose screening ligands with a library of polypeptides in a cell to identify polypeptides that agonize or antagonize receptor bioactivity to create an autocrine system.

Further, one of skill in the art would not have a reasonable expectation of success in combining the teachings of Muthukumaran et al. and Trueheart et al. First, the chimeric receptor of Muthukumaran et al. would not be functional in the yeast cell of Trueheart et al. because the chimeric receptor does not occur in yeast. Also, since the receptor of Trueheart et al. is functionally integrated in the signaling pathway, the chimeric receptor of Muthukumaran et al. could not be used in the signaling pathway of Trueheart et al. without significant experimentation.

Since the Office Action has not indicated where a motivation or suggestion exists in the cited references to combine them and because no reasonable expectation of success exists in combining the cited references, a *prima facie* case of obviousness cannot been established with respect to independent claim 1. Accordingly, applicants respectfully request reconsideration and withdrawal of the obviousness rejection of independent claim 1 and claims 2-6, 14 and 21-23 depending, directly or indirectly, therefrom.

Claims 7, 8 and 10

Claims 7, 8 and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied to claims 1-6, 14 and 21-23, and further in view of Pellegrini et al. (*IDS, Molecular and Cellular Biology*, 9: 4605-4612, 1989).

Applicants respectfully traverse the rejections for the following reasons.

The Office Action indicates that the motivation for combining Pellegrini et al. with Muthukumaran et al. and Trueheart et al. is that "the 6-16 promoter can be fused to a variety of different genes and are tightly regulated by interferon." (Office Action, page 6). "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination." (M.P.E.P. § 2143.01, *citing In re Mills*, 916 F.2d 680, 16 USPQ2d 1430). The statement provided in the Office Action does not provide a suggestion or motivation to combine the cited references, but merely indicates the functionality of the 6-16 promoter.

Pellegrini et al. teaches a genetic selection method for isolating regulatory mutations in a signaling pathway for alpha interferon, but does not suggest or motivate the use of a chimeric receptor, an autocrinic loop or a reporter system. (*See*, Pellegini et al., Abstract). Further, since neither Muthukumaran et al. nor Trueheart et al. suggests or motivates the use of *E. coli* xanthine-guanine phosphoribosyl transferase, a 6-16 reporter or a 2fTGH cell, a *prima case* of obviousness cannot be established. Accordingly, applicants respectfully request withdrawal and reconsideration of the obviousness rejections of claims 7, 8 and 10.

Claim 9

Claim 9 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied to claims 1-6, 14 and 21-23, and further in view of Mizushima et al. (*Nucleic Acids Research*, 18: 5322, 1990). Applicants respectfully traverse the rejections as hereinafter set forth.

Mizushima et al. merely discloses the construction of an expression vector using the EF-1α promoter and does not suggest or motivate the use of the EF-1α promoter in combination with the chimeric receptor, the autocrinic or anti-autocrinic loop, or the reporter system of claim 1. Further, the Office Action has not indicated where in the references of record it is suggested to the use of a HEF1a promoter in the cell of claim 9. Reconsideration and withdrawal of the obviousness rejection of claim 9 is thus requested.

Claims 11 and 15-18

Claims 11 and 15-18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Trueheart et al. in view of Muthukumaran et al. Applicants respectfully traverse the rejections as hereafter set forth.

As previously discussed herein, the combination of Muthukumaran et al. and Trueheart et al. is believed to be improper because no suggestion or motivation exists to combine the cited references. For instance, Muthakumaran et al. is limited to the study of the structure of chimeric receptor complexes and does not teach or suggest screening for ligands. Muthukumaran et al. teaches that the chimeric receptor molecules are functional upon addition of a known ligand, but does not disclose selecting any unknown ligand from a library of compounds. Therefore, one of skill in the art would not be motivated to combine the screening method of Trueheart et al. to search for a compound that creates an autocrinic loop with the chimeric receptor of Muthukumaran et al., since the ligands that bind the chimeric receptors of Muthukumaran et al. are known.

The obviousness rejections are also improper because no reasonable expectation of success exists in combining the cited references to come up with a method as claimed in claimes 11 and 15-18. For instance, since Trueheart et al. discloses a heterologous G coupled receptor in yeast (*See*, Trueheart et al., page 36), wherein the structure of the G coupled receptor is different than the structure of the chimeric receptor of Muthukumaran et al., *i.e.*, the structures of the different receptors have a different number of membrane spans, one of skill in the art would not expect the chimeric receptors of Muthukumaran et al. to function in the screening method of Trueheart et al. that uses the G coupled receptor.

Also, the receptors of Trueheart et al. are not structurally analogous to the chimeric receptor of Muthukumaran et al. because the chimeric receptors of Muthukumaran et al. include a ligand binding domain of one receptor attached to the cytoplasmic domain of another receptor (*See*, Muthukumaran et al., page 4993). Accordingly, one of skill would not expect the structurally distinct chimeric receptor of Muthukumaran et al. to function in the selection methods of Trueheart et al.

With specific regard to the method of independent claim 15, it is directed to screening for

orphan receptors and unknown ligands. No suggestion or motivation exists to combine the cited references as suggested in the Office Action since one of skill in the art would not expect the chimeric receptor of Muthukumaran et al. to function in the yeast cells used in the screening methods of Trueheart et al. The Office Action states "other cells (including eukaryotic cells) can be used as host cells [and] Trueheart et al. also teaches the use of several target receptors." (Office Action, page 7). However, the several target receptors of Trueheart et al. are heterologous receptors, not chimeric receptors. The use of receptors heterologous to the host cell is essential in order to avoid false positives when screening for unknown ligands.

Also, one of skill in the art would not be motivated to combine Muthukumaran et al. with Trueheart et al. since screening for polypeptides that agonize receptor bioactivity is only useful with orphan ligand binding domains, and Muthukumaran et al. does not disclose a functional chimeric receptor with an orphan ligand binding domain. Therefore, without a suggestion, motivation or reasonable expectation of success in combining the cited references, a *prima facie* case of obviousness cannot be established. Accordingly, applicants respectfully request reconsideration and withdrawal of the obviousness rejections of claims 11 and 15-18.

Claim 19

Claim 19 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Trueheart et al. in view of Muthukumaran et al. as applied to claims 11 and 15-18, and further in view of Watowich et al. (*Proc. Natl. Acad. Sci. USA* 89: 2140-2144, 1992). Applicants respectfully traverse the rejections as hereinafter set forth.

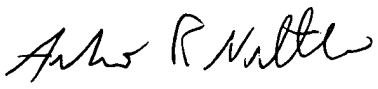
Watowich et al. does not suggest or motivate a method of screening for orphan receptors and unknown ligands. Rather, Watowich et al. is limited to analyzing several mutant forms of EPO-R, and the ability of the EPO-R mutants to form oligomers. (*See*, Watowich et al., Abstract and p. 2141). Further, since neither Trueheart et al. nor Muthukumaran et al. suggests or motivates the use of mutated or genetically modified orphan receptors, a *prima facie* case of obviousness cannot be established with regard to claim 19. Accordingly, applicants respectfully request withdrawal and reconsideration of the obviousness rejection of claim 19.

suggests or motivates the use of mutated or genetically modified orphan receptors, a *prima facie* case of obviousness cannot be established with regard to claim 19. Accordingly, applicants respectfully request withdrawal and reconsideration of the obviousness rejection of claim 19.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the claims define patentable subject matter. It is respectfully submitted that no new matter has been added by the amendments to the specification made herein. If any questions remain after consideration of the instant amendments, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Date: August 22, 2002
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MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

8. (Amended) The eukaryotic cell of claim [6] 7 wherein said reporter system is placed under control of a 6-16 reporter.

11. (Twice Amended) A method of screening [for] a [compounds] compound that [interfere] interferes with the binding of a ligand with the extracellular part of a chimeric receptor and/or with the signaling pathway of the cytoplasmic part of a chimeric receptor, the method comprising:

providing the eukaryotic cell of claim 1;

[reacting a series of compounds with said eukaryotic] contacting said eukaryotic cell with said compound; and

[determining the activity of each element of said series of compounds] selecting cells in which the cell's reporter system is inactivated.

15. (Amended) A method of screening for orphan receptors and unknown ligands comprising:

providing a eukaryotic cell comprising:

a first recombinant gene encoding a chimeric receptor;

a second recombinant gene encoding a compound, the expression of which creates an autocrinic [or anti-autocrinic] loop;

a reporter system that is activated [or inactivated] upon the creation of said autocrinic [or anti-autocrinic] loop; and

[reacting a series of compounds with said eukaryotic cell;

assaying the activity of each element of said series of compounds; and

based on said assaying, determining the presence or absence of orphan receptors and unknown ligands.]

selecting cells in which the cell's reporter system is activated.